UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/244,984	02/04/99	BLACK R	16761/153

HM12/0425

FOLEY & LARDNER
3000 K STREET N W
SUITE 500
WASHINGTON DC 20007-5109

EXAMINER	
ZEMAN, M	

ART UNIT	PAPER NUMBER
1631	12

DATE MAILED: 04/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/244,984	Applicant(s) BLACK ET AL.	
	Examiner Mary Zeman	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39 and 41-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39 and 41-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1631, Examiner **Mary K Zeman**.

Claims 1-39 and 41-65 are pending in this application. Claims 1-39 stand withdrawn from consideration as being drawn to a non-elected invention. Claim 40 has been canceled. Claims 41-65 are under examination. Claims 63-65 are newly added.

This application contains claims 1-39 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's arguments filed 04 February 2001 have been fully considered but they are not persuasive. Any non-reiterated rejections have been withdrawn.

Priority

Applicant is requested to update the priority information at the beginning of the specification. Particularly, Applicant should amend the serial number of the non-provisional application which was converted to provisional. Further, another provisional application is referred to in this statement, but not identified by serial number and filing date, as required.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

In particular: Pages 12, 13, 18, 25, 27 and 29 each recite peptides which are more than four amino acids in length. Claim 47 recites the polypeptide Gly-Ser-$(His)_6$. None of these peptides are followed by a unique sequence identifier as required by the sequence rules. The addition of unique sequence identifiers for these peptides may result in the need for a new CRF

(Computer readable format) and paper copy of the sequence listing, as well as a statement that these new submissions do not contain new matter. If so, these should be submitted as soon as possible. Applicant must respond to this objection for the reply to be considered responsive.

Claim Rejections - 35 USC § 112

Claims 63-65, and claims 41-62 dependent thereon are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This is a new grounds of rejection necessitated by Applicant's amendment.*

In claims 63-65, the phrase "that forms a bond with the catalytic domain" is unclear. What type of bond is formed? Irreversible? Reversible? Chemical or physical? Are the interactions of van der Waals forces considered a bond? Without clarity as to the type of bond to be formed, the "designing" step for designing an associating compound is also unclear. How would such elements be designed, if the nature of the bond to be made is unclear? No positive active steps of the "designing" are set forth such that one of skill in the art would be able to practice the invention. There are no definitions or examples of such designing steps in the specification. Further, the nature of the "determining" step is unclear. Is the predicted association tested *in vitro*? If so, those steps should be recited. If the test is to be done "*in silico*" or by modeling the fit on a computer system, those limitations should be recited in the claims. In fact, the claims do not recite that the claimed methods are computer-based methods at all.

Claims 63-65 and claims 41-62 dependent thereon are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the synthesis of the designed compound prior to the determination of association with the TACE protein. The specification clearly sets forth at page 7, lines 20-25, that the compound to be tested for association with the TACE protein is synthesized prior to making that determination. At page 22, lines 26-27, this point is re-emphasized: "prior to actual *synthesis and testing* of such compound." (emphasis added.) Therefore, the step of synthesizing the designed associating

compound prior to the determining step is an essential feature of the claimed method, and must be included in the claims.

In claim 43, the phrase "wherein the coordinates" should be amended to "wherein the atomic coordinates" to perfect antecedent basis for the dependent claim.

In claims 44-46, 48 and 51, the phrase "said TNF-α-converting enzyme polypeptide" is unclear in its reference. Does Applicant intend to limit the protein of the preamble, or the source of the atomic coordinates?

Claims 52, 53 and 55 recite the limitation "the crystal of said TNF-α-converting enzyme polypeptide" in reference to claim 63. There is insufficient antecedent basis for this limitation in the claim. Claim 63 does not recite "a crystal" such that "the crystal" has basis.

Claims 41-65 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for designing an associating compound based on the co-crystal structure of inhibitor bound, truncated TACE, which contains residues 215-477, the mutations S226A and N452Q, and the added Gly-Ser-$(His)_6$ C-terminal tag, does not reasonably provide enablement for designing other associating compounds to native, and full length TACE. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the reasons set forth in the previous office action, and the reasons set forth below.

As set forth previously, the specification discloses the co-crystallization of a particular associating compound with a specific, non-native TACE. The truncated and mutated TACE is significantly changed from the native sequence. The polypeptide used for the co-crystallization consists only of residues 215-477, has two amino acid changes, and adds a Histidine tag to the C-terminus of the truncated polypeptide. Once the co-crystals with the specific associating compound were obtained, X-ray diffraction coordinates were obtained and reported for only amino acids 219-474 of the truncated polypeptide. The specification does not address the potential steric hinderance, or structure changing effects the missing 214 residues of the TACE polypeptide may have on the resulting crystal structure, nor does it discuss the effects of adding the Histidine tag. Histidines are highly charged, and would be expected to have significant

interactions with its polypeptide environment. Finally, the mutations of a serine and glutamine to less charged residues alanine and glutamic acid would also be expected to have effects on any resulting structure due to the loss of charge.

As addressed previously, crystallization of proteins is a difficult, and non-exact science. Even having the crystal structure of one protein does not necessarily properly predict the nature and structure of a similar or mutated protein. (Gilliland et al. 1996 Current Opinion in Structural Biology Vol. 6 p 595-603) The effects of various changes to the protein are not always predictable, even by sophisticated computer modeling methods that were available at the time of the invention.

Applicant's work published after the filing of the instant application (Maskos et al. 1998 PNAS USA Vol 95 Pages 3408-3412: PTO-1449) draws no conclusions about the native TACE polypeptide, always referring to the catalytic domain, or their truncated co-crystals Further,. The reference indicates that the crystal structure of the truncated polypeptide "shows that TACE is not a typical member of the mammalian ADAMs but stands outside." (P 3412) This would indicate that conclusions or ideas generated for the ADAMs family of polypeptides may not be applicable to TACE catalytic domain polypeptides or native TACE polypeptides. This is a critical piece of information for the design of associating molecules. Maskos et al further separate the TACE polypeptide structure from known families of polypeptides in the discussion of the MMPs. Maskos et al. indicate that the structural homology between the catalytic domains of TACE and the MMP's is significantly lower than previously thought. This indicates that previous homology and structural design experiments were incorrect in their prediction that TACE had high structural homology to this family of known proteins. Finally, Maskos et al. state that "TACE exhibits, however, several structural peculiarities regarding surface charge and shape, which may enable the design of potent selective synthetic inhibitors." (emphasis added) This conclusion underscores the unpredictability of the prediction of protein structure, and the results of modeling inhibitors based on that prediction.

The specification fails to provide working examples of the design of other inhibitors, or the design of other associative compounds that subsequently were shown to inhibit or associate with the *native* TACE polypeptide. While working examples are not, per se, required, the specification must provide an enabling disclosure for the invention as it is now claimed. While

the skill in the art of protein crystallography and computer structure analysis is high, that same art is highly unpredictable, and conclusions reached about one family of proteins cannot necessarily be applied to another, even if there appears to be structural homology from computer predictions. The X-ray structure of the protein in question is required in order to assess those predictions with any accuracy. The specification provides only the x-ray structure of the truncated and mutated TACE polypeptide, therefore, the scope of the pending claims is not enabled.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 63, 41, 44, and 56 remain rejected under 35 USC 102(b) as being anticipated by Gomis-Ruth et al. (1998). *To the extent that this rejection applies to newly added or amended claims, it is based solely on Applicant's amendment.*

Claim 63 is drawn to a method of identifying a compound which associates with a TACE polypeptide, by using atomic coordinates from a crystallographic analysis of TACE, designing the compound, and determining whether it associates. No particular crystal structure is claimed. No particular design or determination steps are recited. The specification discloses that such design and determination steps were quite well known in the art.

As set forth previously, Gomis-Ruth et al. disclose atomic coordinates of a TACE polypeptide which are derived from a crystallographic analysis of adamlysin which was used to produce a theoretical crystal structure for the TACE polypeptide (See figure 7). Applicant argues that since Gomis-Ruth does not disclose an actual crystal structure for TACE, it cannot be anticipatory, however, as set forth above, the rejected claims do not require that particular structure, or any other particular structure. Gomis-Ruth et al. synthesize Pol647 and Pol656 as potential associating compounds, and model their interactions with the theoretical crystal structure. Again, the rejected claims do not set forth that the determining step must actually be performed (for example, in a laboratory) with the actual TACE polypeptide- an "in silico" determination meets the limitation of the claims. Gomis-Ruth et al. show that the designed compound Pol656 occupies the S1' pocket of the TACE structure, as was predicted by analysis

of the theoretical crystal structure. Gomis-Ruth et al. is a proper 102(b) reference, as it would appear to have been available February 1, 1998. Applicant has priority to February 4, 1998 under 35 USC 119(e). Therefore, Gomis-Ruth et al. meets the limitations of the above-rejected claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028.

The fax number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose telephone number is (703) 305-3524.

mkz
April 17, 2001

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
~~GROUP 1600~~
AU 1631